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the case where inheritance is sharply alternative, but subject to extremely great fluctuating variations. It is open to question whether blending characters of this sort found in many breeds may not have been created by selection from masses of fluctuating variations. It will be important to know further whether or not these extreme fluctuating series have had their origin in mutations. Not improbably, as de Vries has in part suggested, one-sided variation curves indicate the occurrence of mutations of this sort.

*The Mutation Theory From the Standpoint of Cytology:* EDWIN G. CONKLIN, professor of zoology, University of Pennsylvania.

I. The mutation theory is founded upon the idea that mutations are primarily germinal, that they arise in one or both of the sex cells and only later appear in the adult organism. In contradistinction to certain theories of evolution which are concerned chiefly with the modifications of adult structures, the mutation theory is primarily concerned with modifications of the germ, and here it comes into direct relation with the science of cytology.

De Vries tells us that the foundations of the mutation theory were laid in his doctrine of intracellular pangenesis. Like Darwin, Galton, Weismann and many others, he recognized the fact that the method of evolution is at bottom a problem of inheritance and that, in the words of Osborn, 'When we have reached a heredity theory that will explain the phenomena of inheritance, the method of evolution will itself be a thing of the past.'

It seems like a mere truism to affirm that the evolution of animals and plants must be accompanied by an evolution of their germ cells, and that the principal problem of evolution is not how modifications are produced in adults, but how they arise in

the germ. And yet with few exceptions previous theories of evolution have concerned themselves only with the transmutations of adult forms and have paid no attention to the modifications of the egg or sperm or embryo. The mutation theory is a theory of the evolution of organisms through the evolution of their germ cells and it is, therefore, founded primarily upon cytological phenomena.

An antecedent objection to any such theory is the very general opinion that the germ cells are composed of 'simple, undifferentiated protoplasm' and that they do not contain specific morphological elements upon which evolutionary forces might act. However, such a view is supported neither by observation nor by the latest and most careful experiments. We know that the cell is vastly more complex than was assumed a few years ago, and there is no good reason for supposing that all of its visible structures are now known. The fact that fragments of eggs may in some instances give rise to entire embryos does not necessarily imply, as is usually assumed, that the egg is undifferentiated. In eggs, as in adult forms, the degree of differentiation may be largely independent of the power of regeneration or regulation, and certainly such experiments do not nullify the most positive and direct evidence, drawn from many sources, as to the complexity of the germ.

Extensive studies which have been made upon the structure of the nucleus have brought to light a degree of organization in this part of the cell which was wholly unexpected. It has long been known that in any given species the number of chromatic threads or chromosomes in the nucleus is constantly the same in all kinds of cells, except in the last stages of the formation of the sex cells, where the number is one half the normal; in the union of the egg and sperm nuclei in the fertiliza-

tion the normal number is again restored. Van Beneden, Boveri, Hertwig and others have shown in the most convincing manner that these chromosomes are the principal seat of the material substance concerned in hereditary transmission, and recently Boveri has determined that the several chromosomes are individually different in the heritable qualities which they bear. Coincidentally with this notable discovery Montgomery found that the reduction of the number of chromosomes in the sex cells is effected by the union of chromosomes into pairs and he showed good reason for believing that one member of each pair came from the father and the other from the mother. This conclusion was confirmed and extended by Sutton, and he, as well as others, pointed out the suggestive fact that in the maturation divisions immediately preceding the formation of the ripe egg or sperm only one chromosome of each pair goes into each mature germ cell. This parental purity of individual chromosomes in the sex cells corresponds to the purity of parental characters in the experiments of Mendel and the chance combination of these chromosomes into pairs in fertilization corresponds with the combinations of qualities (the Mendelian ratio) in alternate inheritance. These remarkable discoveries as to the organization of the nucleus demonstrate that the germ cells are by no means simple and undifferentiated, as has often been affirmed, but rather that they contain numerous visible morphological elements, each of which has a particular rôle in hereditary transmission, and they suggest that modifications of these elements, however produced, are the real causes of evolution.

Much work has also been done upon the differentiations of the cytoplasm in the egg cell (obviously the sperm is unsuitable for such a study); with few exceptions the earlier experimental work led to the con-

clusion that the cell substance was isotropic and undifferentiated. However, many careful observations have shown that in the case of many animals the cytoplasm is visibly differentiated in certain areas of the egg and that the substances of these areas give rise in the course of development to particular organs or parts of the embryo. It is now known that in the eggs of a considerable number of animals belonging to several different phyla all the axes and planes of symmetry of the future individual are marked out in the unsegmented egg, and in the case of certain annelids, mollusks, echinoderms and ascidians it has been discovered that the substances of the ectoderm, the mesoderm and the endoderm are visibly differentiated in the egg before cleavage begins. In certain ascidians I have found that all the principal organs of the larva, viz., the muscles and mesenchyme, the gastric endoderm and general ectoderm, the nervous system and notochord, are all represented in the two-cell stage by visibly distinct substances which are definitely localized in the egg. These facts show that in certain groups of animals there is such a thing as a morphology—not merely a promorphology—of the ovum and they demonstrate that there are morphological elements in the cytoplasm upon which evolutionary forces may act.

It is a matter of prime importance to know whether the nucleus contains the only hereditary material carried over from one generation to another or whether certain characters, such as polarity, symmetry and the localization of organ bases in the egg, may not have their seat in the cytoplasm. It is as yet too soon to make any positive assertions on this point but the evidence seems to favor the view that the nucleus is at least the principal seat of the inheritance material. Even in cases where the cytoplasm of the egg is so highly differentiated as in ascidians this conclusion

probably holds good. The three principal kinds of protoplasm of the ascidian egg before cleavage are the ectoplasm which gives rise to ectoderm, the mesoplasm which produces mesoderm and the endoplasm which becomes endoderm. Each of these three substances is derived in part from the nucleus of the egg; the ectoplasm comes from the egg nucleus at the beginning of the first maturation division, the other two from the nucleus at an earlier stage in the oögenesis. In every cycle of division a large amount of chromatic material escapes from the nucleus into the cytoplasm and I have found in mollusks and ascidians that this substance is then differentially distributed to different areas of the egg and that it gives rise in part to the principal formative substances of the embryo. These facts lend support to the hypothesis of intracellular pangenesis proposed by de Vries; they show that even though a certain number of general differentiations may be transmitted through the cytoplasm, such as polarity, symmetry and localization, nevertheless the mechanism exists for the nuclear control of the cell and they thus afford a means for harmonizing the facts of cytoplasmic organization with the nuclear inheritance theory.

We find, therefore, that the germ is by no means simple, even if we consider only the visible structures of the cell, and that its organization is sufficiently complex to exercise a determining influence upon development and evolution. Similarities in the character and localization of the material substances of the egg must be the initial causes of all similarities or homologies which appear in the course of development. Modifications of this germinal organization, however produced, are probably the immediate causes of evolution.

II. If we inquire how such modifications of the germ arise and what the particular modification is which is associated with a

certain mutation of the adult organism, we pass from the region of observed fact to one of hypothesis, for in only a few instances have such germinal mutations been observed. Nevertheless, enough is known regarding the organization of the germ cells to warrant our hazarding a 'shrewd guess' as to the nature of these germinal mutations. The nuclear inheritance theory points to some modification in the structure, number or distribution of the chromosomes or of the elements of which the chromosomes are composed as the initial cause of mutation. The fact that the Mendelian ratio in alternate inheritance corresponds to the ratio of chromosomal distribution in the maturation and fertilization of the egg indicates that in such chance distribution of these chromosomes we have the principal cause of the law of alternate inheritance, as Wilson, Sutton, Cannon and others have pointed out. It may also be reasonably inferred that in this chance distribution of chromosomes we have one of the most potent causes of individual variations.

It is well known that the disappearance of characters does not necessarily imply their final loss; many heritable qualities remain latent through one or more generations, only to appear as active characters in subsequent generations. In such cases it is probable that the material bearers of these qualities also remain latent, though we are wholly ignorant of what constitutes latency as contrasted with activity in chromosomes.

Relatively little is known as to the factors which determine the number of chromosomes or as to the effect of varying numbers on adult organization. Montgomery concludes from his studies on the Hemiptera that certain chromosomes are in the process of degeneration and disappearance in these animals. In this case the heritable qualities which were borne by these chro-

mosomes would also disappear, thus constituting a case of 'regressive mutation' in the terminology of de Vries. In other cases there has evidently been an increase of chromosomes in some species as compared with others; though whether this increase is due to the division of originally single chromosomes, or to the addition of new ones through abnormalities of division or distribution, or through hybridization, can not now be determined. Irregularities in the number and distribution of chromosomes are by no means uncommon and in the case of hybrids are very frequent, as has been shown by Juel, Guyer and Cannon. By an increase in the number of chromosomes or in the number of elements of which a chromosome is composed the sum of the heritable qualities would probably be increased, thus constituting, in the language of de Vries, a 'progressive mutation.' There is no evidence and no probability that new chromatic elements are ever added to the nucleus from the cytoplasm, or that they ever arise *de novo*. Such new elements must arise through new combinations of old elements, either, as de Vries considers, by an actual interchange of *Anlagen* (material particles) between the pairs of maternal and paternal chromosomes, or, as Haecker supposes, by an interchange of grandparental parts of chromosomes, or through hybridization or irregular mitoses. Guyer has shown that the divisions of the chromosomes are frequently or usually irregular in hybrids and he suggests that such irregular mitoses may add or subtract certain chromosomal elements and thus constitute the basis for a mutation. Such cases are, however, almost entirely hypothetical and at present we are compelled to admit that we do not know how mutations arise or first become manifest in the chromatin.

As regards the cytoplasm, I have shown reason for believing that it is composed in

part of escaped nuclear material and that the mechanism, therefore, exists for the nuclear control of the entire cell. The organization of the cytoplasm is chiefly manifest in its polarity, symmetry and the localization of unlike substances. There are reasons for believing that many bilateral animals are characterized by fundamental similarities in the polarity and symmetry of the unsegmented egg; the types of localization of organ bases are, however, very different in different phyla; in particular the localizations in the eggs of ctenophores, nemerteans, echinoderms, annelids, mollusks and ascidians are thoroughly characteristic of each phylum, and except in the case of the annelids and mollusks there are few similarities between these types. Nevertheless, it is possible that certain of these types may have been derived from others; in fact, such transformations might be accomplished far more easily in the egg than in the adult.

Despite the evident and almost insuperable difficulties involved, certain zoologists have not hesitated to indicate how the adult form of one phylum might have been derived from the mature form of another; thus we have the coelenterate, the nemertean, the echinoderm, the annelid and the arthropod hypotheses as to the origin of the vertebrates, and in each of these cases by stupendous transformations, degenerations and new formations of the adult form of the invertebrate in question the vertebrate is supposed to have sprung into existence fully formed and panoplied, like Minerva from the brain of Jove. In all these speculations fancy occupies so prominent a place and facts are so scarce that it is no wonder that the whole 'phylogeny business' has come into disrepute. Nevertheless, the evolution idea compels us to assume that there are relations more or less remote between all phyla and that some must have come from others by natural processes.

Without attempting to defend any of the hypotheses mentioned it may here be pointed out that relatively slight modifications in germinal organization would convert one type into another.

A distinguishing characteristic of the mutation theory is the recognition of elementary characters or properties which manifest themselves in many separate parts of the adult, as, *e. g.*, the presence or absence of hairs or certain colors; if mutations are germinal the widespread distribution of such characters in the adult are easily explained. Relatively slight modifications of the germ, however produced, may lead to profound and widespread modifications of the embryo and adult. I have elsewhere shown reason for believing that the cause of inverse symmetry which occurs regularly among some species and occasionally among all, man included, is to be found in the inverse organization of the egg, and that this inverse organization may be due to the maturation of the egg at opposite poles in dextral and sinistral forms. This case shows that one of the most remarkable and far-reaching forms of variation with which we are acquainted is the result of relatively slight alterations in the localization of germinal substances in the unsegmented egg.

One of the principal difficulties in explaining the origin, on evolutionary grounds, of different phyla has been the dissimilar locations of corresponding organs or parts. These difficulties are well illustrated by the theories which attempt to derive the vertebrates from the annelids, or from any other invertebrate type. If evolution takes place through transformations of the germ rather than of the adult, it is no more difficult to explain the different locations of corresponding parts in these phyla than their different qualities. Changes in the relative positions of parts which would be absolutely impossible in the

adult, may be readily accomplished in the unsegmented egg, as is shown by cases of inverse symmetry. The question is here raised whether some similar sudden alteration of germinal organization may not lie at the basis of the origin of new types.

*Mutations:* THOMAS DWIGHT, Parkman Professor of Anatomy, Harvard Medical School.

It has been clear from the beginning that evolution, if it be a power at all, must work either by minute modifications or by more or less sudden changes. Darwinism is essentially the doctrine of minute modifications increased by selection and controlled by the survival of the fittest. Darwin insisted most strongly on the importance of minute modifications. While holding that 'strongly marked variations' might modify a species without the help of any selection at all, he absolutely denied any sudden changes of importance such as lie at the bottom of the mutation theory. 'Natural selection,' he wrote, 'acts only by the preservation and accumulation of small inherited modifications'; and he asserted that it would 'banish the belief of the continued creation of new organic beings or of any great and sudden modifications of their structure.'

The mutation theory of sudden jumps and, it may be, of long jumps, is far from new; but it is de Vries's merit to be able to show by demonstration what before was only theory. His hypothetical 'pangens' by which the changes are said to be brought about need not be discussed here. A radical difference between the two theories is this: Darwinism pure and simple is essentially fortuitous; it aims in no particular direction, there is no goal; while mutation by producing suddenly a new species, or at least a subspecies, implies the existence of a type and of a law which under certain conditions becomes operative.